TOXEMIA FROM THE STANDPOINT OF PERVERTED METALBOLISM.

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This subject of toxemia has become, in recent years, of great importance. So varied are the conditions which, owing to vague etiology, have been classified as toxemic or toxic in character, that a brief discussion of a few of them seems not ill-timed. I cannot go into detail regarding many of these conditions, but must limit myself to these better known, leaving those of indefinite etiology with mere mention.

Definition. So uncertain have been the ideas regarding toxemia that it seems advisable, in the beginning, to define what is meant by this term. Toxemia is a condition characterized by the overloading of the blood with normal or abnormal products of food or tissue metabolism. This condition, therefore, is purely endogenous in character, and is sharply separated from those conditions associated with toxic symptoms due to exogenous products as well as from those toxemic states arising in the course of infectious diseases. Of course, the toxemia related to abnormal intestinal activity may be due to bacterial action to some extent, but the bacteria concerned in such processes are normal habitants of the intestinal tract, and may, therefore, be considered aside from those producing the acute infections. Toxins elaborated by the activity of specific microörganisms upon the various classes of tissue of the body, cause, oftentimes, such an intense poisoning of the system that death results, but this specific toxemia is not under discussion in this paper. Time will not permit a differentiation, both chemical and pathological, of these two types of toxemia; I can do no more than refer to the fact that in all infectious diseases specific toxic products are formed, the influence of which depends upon the resistance of the system as characterized by the presence and activity of antibodies, such as antihemolysins, antitoxins, anti-agglutinins, opsonins, etc. These subjects are becoming of prime importance in the study of infections, but are beyond the scope of this paper.

It should be further remembered that excessive normal or abnormal activity of one organ may so influence the activity of other organs that a toxemia may follow as a result of perverted secondary metabolism. The close relation or coördination of the various tissues of the body has been well treated by Starling in his assumption of the various "hormones."

Perverted Metabolism. Accepting, then, that the toxemia under discussion is endogenous in character, is usually non-bacterial, and is influenced by the inter-relations of the many organs of the body, is there any basis for the belief that it is due to perverted metabolic activity of any organ or group of organs? It is more or less common, in these days, to hear of intestinal, hepatic, renal, thyroid, orchitic, and other toxemias, as well as of those conditions occasionally accompanying more or less physiological states, such as pregnancy. It is evident, therefore, that such conditions are associated, in the minds of the profession, with abnormal activity of the organ in question. It is reasonable to suppose, and definite proof can be given, that abnormal activity, that is, perverted metabolism, of any organ results in the overloading of the blood with products which may, *per se*, lead to various symptoms of the toxemic type, or may so influence the activity of other organs that abnormal relations obtain. Moreover, the activities of many organs, depending as they do on the presence of certain substances elaborated by other organs, and passed by them into the blood stream, are influenced to abnormal activity by their absence, due to disease or to perverted metabolism of the coördinated organs. It is necessary, in support of this view, only to cite the influence of the thyroid, ovary, testicle, pancreas, suprarenal, and hypophysis on the general body functions. Remove them and the results are well known.

INTESTINAL TOXEMIA. In the study of this condition we have to consider several factors. It is evident that the activity of the intestinal juices is dependent on the quality and quantity of the food introduced, the quality and quantity of the intestinal juices, the power of absorption, and the motility of the intestine. Normally, no great variation in the decomposition processes, both those due to the intestinal ferments and those due to intestinal bacteria, is observed. Yet any abnormality in any of the factors above mentioned will lead to markedly abnormal decomposition processes. Thus the intake of an excessive amount of food or drink leads first to disturbance of the gastric functions, as shown by the symptoms of nausea and vomiting, and later to marked intestinal disorder, as evidenced by the symptoms of enteritis. While such disturbances do not, necessarily, lead to general symptoms, yet the common complaint of weakness, headache, rapid, weak pulse, etc., show that a general influence is present. Moreover, a direct effect upon the intestinal activity is observed after the intake of a large amount of food. The digestive powers of the juices are pushed to the limit to take care of the excess, but unless abnormal motility of the bowels is present, this excess cannot be handled. We thus observe an effort on the part of the bowel to overcome these effects. Diarrhœa, under these conditions, is a conservative process, since without it the digestive juices cease to act, according to the law that an accumulation of the products of activity of an enzyme will retard or prevent further activity. In case the motility of the bowel is normal, the food remains in a partly digested state, and is then subject to the activity of the bacterial flora of the intestines. Such latter activity is not the same as is that of the digestive juices, except to a certain degree, and abnormal products are formed. The ordinary processes which occur in the bowel abnormally are fermentation of the carbohydrates, putrefaction of the proteins, and conversion of the fats to lower fatty acids. Normally fermentation occurs in the lower parts of the small intestine, while the putrefactive processes take place, almost exclusively, in the large bowel. Occasionally we find these latter changes in the small intestine, and in such cases the decomposition products, as found in the urine, are much increased, owing to the greater absorptive power of the small bowel. It is clear that an abnormal condition of the digestive juices will lead to a lessened digestive, and, hence, to a lessened absorptive power of the bowels. Without such conditions food has little energy value, and symptoms of undernutrition slowly but surely supervene. I cannot discuss the metabolism of this condition, but I can say that perverted metabolism of all organs is present.

Toxemia of intestinal origin is due to the absorption of abnormal amounts of normal products or to normal absorption of abnormal products. By this I mean that excessive intake of food or deranged intestinal activity will lead, under certain conditions, to absorption of large amounts of the products normally or abnormally present. This excess taxes the liver in its effort to convert the nitrogenous products into urea, in its effort to elaborate the carbohydrates into glycogen, and in its attempt to furnish sufficient bile to permit of the absorption of the fat. Failing in this, the liver must allow the excess to pass from it in the unelaborated state. Such a condition overloads the blood with purin bodies, with amino-acids, with sugar, and with other substances, which exert toxic effects on the system, in case the accessory organs are unable to handle them. I cannot discuss the influence of excess of uric acid or of sugar in the blood beyond the statement that well known conditions arise from such an excess.

It is, however, with the abnormal decomposition products of intestinal activity with which I desire to deal in this discussion. Where can we draw the line between normal and abnormal decomposition in the bowel? That the products formed may exert some toxic action on the system is true, but we must not exaggerate these influences. We are indebted to Bouchard for the doctrine of intestinal auto-intoxication, and, since his publications, a general belief has prevailed that decomposition in the intestines plays a large role in the production of disease and errors of metabolism. The question is very apropos, To what extent and under what conditions may normal products of putrefaction and fermentation cause disease? The number of putrefactive products which occur in the intestine only under pathological conditions, and to which any toxic action can be attributed, is remarkably small. Skatol, indol, etc., may cause headache, neuralgia, neurasthenic symptoms, etc., yet, as Rovighi has shown, symptoms of poisoning are evident in dogs only when 1 gram per kilo is injected. The production of acetone and diacetic acid in the bowel has been assumed by Peters, Litten, von Jaksch, Lorenz, and others to be a sign of intestinal intoxication leading directly to a state of acidosis, which markedly affects the general metabolism. Keller, Pfaundler, Czerny, and others have made this condition accountable for the cyclic vomiting in children. We now know that, although these acetone bodies are formed to some extent in the bowel, yet they occur as common accompaniments of starvation, especially as regards the carbohydrate foods. Ptomaines, such as putrescin and cadaverin, have been found in the urine and feces by Udransky and Baumann, Stadthagen and Brieger in cases of cystinuria, which were associated with abnormal protein decomposition. It is quite possible, when the true nature of this disorder of metabolism is known, that these substances may be found to be derived from abnormal tissue metabolism and not from that of food products.

The subject of the influence of these decomposition products on general metabolism is still an unknown field. Little is found as to the effects of such substances. While it is true that abnormal decomposition in the intestine is associated with abnormal products, yet none of these products, so far isolated, has been proved sufficiently toxic to account for the general effects of such disturbances. It seems to me that the results observed following intestinal disorders are to be explained by the effect of the products of abnormal decomposition upon the metabolism of other organs rather than by the direct effects of the products themselves. The question of intracellular activity is more fertile, in my opinion, as a field of research than is the constant study of the products of bowel activity. No question can be raised that intestinal toxemia occurs, but its causation is still unsolved. It may be that some product, at present unknown, may be found that is sufficiently toxic to account for the effects, yet the secondary metabolic effects seem to me the more plausible.

HEPATIC TOXEMIA. The liver, owing to its many functions, is one of the most important organs of the body. While its secretory activity is confined to the elaboration of bile, its so-called internal secretory functions are of great influence upon the general metabolism. It is in the narrow space of the liver cell that we find localized the formation of glycogen from sugar, the conversion of the amino-acids and ammonium compounds into urea, the neutralization of extrinsic and intrinsic toxins, the conjugation of aromatic bodies with sulphuric and glycuronic acids, as well as the storing up of fatty acids and soaps. Any disturbance in any of these functions is promptly felt by the system as a whole.

In the discussion of toxemia of hepatic origin I shall not consider the toxic effects due to stagnation of bile. The formation of bile is a specific vital function of the liver, and it is self-evident that its involvement or abolition, as a result of pathological changes in the organ, cannot continue without severe reactions upon the system in the sense of an auto-intoxication (Weintraud). Such metabolic results of jaundice of short or of long standing are too well known to require elaboration. The bile acids, with their known effect of producing hemolysis and slowing the pulse, will likewise be passed over, as such activity is not due to a direct disturbance of metabolism, but rather to a specific action of these compounds. While it is true that jaundice, acute yellow atrophy, cirrhosis, phosphorus poisoning, etc., have definite influence upon the local and the general metabolism, yet in this discussion I do not have reference to specific disease of the liver, but rather to the toxemia as a result of insufficiency of this organ. It may be said that there are no functional disturbances of the liver cells that are pathognomonic of absolutely definite changes in the hepatic parenchyma. As every disturbance of the activity of the cells influences the proper performance of other functions, a number of phenomena are combined in this symptom-complex of hepatic insufficiency.

One of the most important functions of the liver is its antitoxic power. As Weintraud has well said: "The antitoxic functions of the liver may be, to a great extent, comprehended by recognizing a protective action in each of the numerous metabolic indications by which the functional activity of the normal liver cell manifests itself, and by seeing an intoxication in the disturbance of these functions. At all events, the normal composition of the tissue juices is altered, and they depend upon hepatic integrity for their adequate maintenance. Just as the synthesis of urea from the toxic ammonia permits the harmless urea to be excreted, so the formation of glycogen from the carbohydrates prevents an overloading of the system with glucose. The poisonous products of digestion of protein are converted, during their passage through the liver, into non-toxic compounds, while the free fatty acids and soaps, which arise in intestinal digestion of fats, and which are toxic in large amounts, are retained and stored up in the liver. The formation of bile likewise frees the body from other injurious products of cell activity." Although there may not be enough constancy in the so-called hepatic insufficiency to warrant the assumption of a clinical symptom-complex, yet there are many evidences of this condition, which lead us to believe that a toxemia may arise from such a source. Few of the tests advanced as diagnostic of such a condition have stood the fire of criticism, but the finding of Strauss, that levulosuria follows the ingestion of 100 grams of levulose during fasting, has remained fixed.

While it is difficult to say just how far other organs may be functionally influenced by the toxic action arising from disturbances of the liver, there can be little question that certain toxemic symptoms may be manifested by disorder of any of the hepatic functions.

Although I cannot go into a discussion of the hepatogenous form of diabetes, due to the insufficiency of the liver to handle the sugar brought to it by the portal vein, or of the various disorders related to the so-called uric acid diathesis, yet these should be borne in mind. It is evident that any perversion of the normal functions of the liver will lead to the accumulation of abnormal products. Normally, autolytic processes are going on in the liver cells, which result in the formation of definite products. These are rendered inert by the same liver cells that produce them. In other words, the liver cell is capable of breaking down and resynthesizing its own constituents. These autolytic products are, as Magnus-Levy has shown, of the acid type, and pass into the circulation unmolested, providing the liver is not capable of exerting a sufficient antitoxic effect. Thus arises a condition of acidosis, whose influences are fairly well known. It is not to be understood that the liver, under abnormal conditions, is the only seat of formation of such bodies, but it is one of the most important. Usually the pathological changes associated with such processes are fatty in nature, as evidenced by the fact that in phosphorus poisoning, acute yellow atrophy, and delayed chloroform poisoning, fatty degeneration of the liver is associated with an increased output of amino-acids and acetone bodies.

A second series of changes which give rise to signs of hepatic toxemia are those associated with disturbance in the conversion of amino-acids, etc., into ammonia, and thence into urea. Here we find an ammoniemia along with irregular autolysis, leading to an increased acid formation either of the amino or oxy series. This condition is quite distinct from that discussed above and has a separate function of the liver to deal with. The combination of these two conditions has lead to the assumption by Croftan and others that the liver is more at fault in the causation of uremia than is the kidney. Yet we must remember that were the kidneys not involved uremia would not occur, although symptoms somewhat resembling it may obtain. The general metabolic effect of such a condition is more in the foreground in such cases than is the hepatic or renal disorder, yet the hepatic insufficiency is, in some degree, accountable for the overloading of the system with such products, while the renal insufficiency prevents their excretion.

Another class of hepatic toxemias is found in a low-grade infection of the gall-bladder. I have recently seen, through the courtesy of one of our leading physicians, a patient who had been treated for ten months for dilatation of the heart without the slightest effect. Indeed, the trouble had progressed. On simple drainage of the gall-bladder, although no symptoms pointed to this organ, the cardiac symptoms became better, and within a few days had almost subsided, the heart being reduced to about normal size. This points, it seems to me, to some obscure toxemia, with the gall-bladder as its source. As the bile excretes many of the toxic substances carried to the liver, it seems rational to suppose that, through some perversion of metabolic activity, such products, possibly of bacterial origin, were either not excreted into the bile, but were passed into the circulation, bringing about a toxemia, or, being excreted, a low grade inflammation of the gall-bladder ensued, which may have induced the condition found. We all know that the myocardium is extremely sensitive to untoward influences, so that the above assumptions do not seem far-fetched.

We must grant, therefore, that many metabolic perversions of the liver may lead to definite toxemia, although this may not always be manifested by a clear etiology. Certain it is that some of these toxemias of hepatic origin are associated with urinary and blood findings, which are not, it is true, pathognomonic, but do point to the probable source of the trouble.

Renal Toxemia. That toxemia of renal origin occurs is unquestioned, but the cause of such a state is unknown. All gradations of such intoxication, from the intense acute uremic state to the slow chronic form, are observed. The theories advanced regarding the causation have for the most part as a basis the idea of overloading of the blood with urinary constituents as a result of an insufficient kidney. Opposed to these theories are those that hold that hydremia, with resulting œdema of the brain, is at the bottom of the symptomatology. These latter ideas are especially advocated by Rees and Traube, but do not seem convincing, inasmuch as certain factors assumed by the advocates are at times missing, and hence cannot be regarded as causative in all cases. We all know that retention of almost every constituent of the urine has, at one time or another, been held to be the etiological factor in uremia. One by one these substances have been abandoned, until now we cannot grant that anyone is specific in the causation of this group of symptoms. From the time that retention of urea was advocated by Wilson until the list had been exhausted by Bouchard in his assumption of organic urotoxins, we have been obliged to change our ideas of the factors responsible for this trouble. Opposed to these views are those of Frerichs, Demjankow, and the closely related one of Treitz, which assumes an ammoniemia as the causative agent. Strauss found that ammonia was increased in the blood, but at the same time nitrogenous bodies, other than albumin and urea, were present, which must play a role in the etiology. He shows that, while the salt content of the serum in uremia does not change, the amount of nitrogenous constituents contained in the hydremic serum, that is, the retention nitrogen, is, as a rule, increased to a great extent. In connection with this work of Strauss one must mention the findings of Gumlich and Richter, that ammonia, alloxur bodies, and extractives were markedly increased in the urine of uremics. As von Noorden states: "A thorough inquiry into the localization of these substances and into their toxic action in cases of renal insufficiency is much needed. It will also be necessary to ascertain how and to what extent glands, such as the thyroid and suprarenals, react to the intoxication; whether by insufficient or excessive secretion, or by the production or neutralization of the products of metabolism. When we are acquainted with all the factors which probably go to determine the appearance, progress, and prevention of uremia, it will no longer seem strange that it cannot be correctly estimated or adequately explained either by the deficit in the metabolic balance or by quantitative analyses of the blood." It is certain that no definite explanation of this toxemia can be given at present, although many attempts have been made to account for it.

It is well known that complete anuria may obtain and yet no symptoms of toxemia be present. This should prove that it is not alone the retention of waste products that brings about this syndrome, but rather some unknown influence acting upon the general or special metabolic activity. Toxemia of renal origin surely, is a clinical entity, but just what the mechanism of the process is is still unsolved. It may be that the little understood secretion of the kidney may be at fault, but until more is known regarding this speculation is superfluous.

Thyroid Toxemia. The thyroid is of great importance in the general metabolic activity of the system. When this organ is lacking, owing to disease or to removal, a marked lowering of the general energy relations ensues, while in cases in which its function is exaggerated a great increase in the total consumption of energy is noted. There is no organ, with the possible exception of the working muscle, which exerts such an influence on the energy relations as does the thyroid (Magnus-Levy).

The thyroid excretes in its colloid substance an active product, thyreoglobulin, which is combined with the specific iodothyrin. This substance is, no doubt, the one to which a great deal of the influence of the thyroid is due, yet no absolute data bearing on this are at hand. The internal secretion of the gland finds its way through the lymph stream into the blood, whence it passes to the various organs upon which its influence is exerted. It is known that definite signs of toxemia follow both the excessive and the deficient action of this organ. It is necessary only to cite the symptoms in a well marked case of Basedow's disease, such as hyperidrosis, exaggerated reflexes, restlessness, tachycardia, tremor, etc., as well as those of myxœdema or of cachexia strumipriva, to carry my point. Just what are the etiological factors at the bottom of these conditions is unknown, and it seems useless, in the present state of our knowledge, to speculate. Two theories have been advanced to account for the action of this gland, but neither seems convincing. The first, the so-called secretion theory, is that failure of the internal secretion of this gland causes not only quantitative but also qualitative changes in the metabolism, so that poisonous products appear which either do not obtain normally, or are "disintoxicated" by the thyroid secretion. The second theory, the so-called antitoxic theory, varies from the first in that the antitoxic action takes place in the thyroid itself through the influence of the specific iodothyrin.

This internal secretion of the thyroid is known more by its effects than by its properties after isolation. Even the iodothyrin is not a definite chemical entity, as it has been shown to have varying amounts of iodine. That excessive activity leads to different results from deficient function is evident, yet the variations may be more quantitative than qualitative.

Many other conditions, which may be classed as toxemic, are observed following perverted metabolism of the suprarenal glands, of the hypophysis, of the ovaries, and of other organs. The symptoms of such toxemias are not so well marked, in all cases, that an absolute diagnosis may be established, yet the etiological factor at the bottom may often be discovered by careful consideration of the normal functions of the various organs mentioned. It is true that the function of some of these organs is unknown, and that their internal secretion is even more obscure, yet we may hope that research will unravel these mysteries and throw a definite light on the origin of these obscure toxemias.

CONCLUSIONS. Toxemia, aside from that following the acute or chronic bacterial processes, is always of metabolic origin. The toxemias under discussion are more the effects of a general metabolic perversion than of a direct organic disorder. A specific toxemia, in the sense that it is due to a specific substance, is unknown in the class of toxemias discussed.

THE RELAXED KNEE-JOINT.[1]

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DURING the last few years great advances have been made in the diagnosis of the non-tuberculous chronic joint diseases, and, in consequence thereof, in their treatment. These advances have been made possible by the use of the Röntgen rays, by the laboratory study of diseased joints, as well as by the material obtained by operations. Indeed, these operations themselves have been the source of much enlightenment. We have learned thus to distinguish and to recognize the clinical meaning of the different forms of infectious

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[1] Read at a meeting of the Southern Surgical and Gynecological Association, New Orleans, La., December 18, 1907.